REMARKS

Claims 1-6, 12, 14, 19-24, 26, and 30-31 are amended herein. Support for the amendments can be found throughout the specification. For example, support can be found at least at page 5, lines 23-26; at page 9, lines 11 and 12; at page 4, lines 20-29; and at page 9, lines 13-20. Claim 32 is canceled herein. Claim 33 is newly added. The amendments to the claims are made in order to expedite prosecution and/or correct typographical errors and are not an acquiesence to any of the outstanding rejections. Applicant reserves the right to pursue the subject matter of the previously presented claims in future prosecution. Claims 1-31, and 33 are currently pending.

I. Outstanding Rejections

Claims 1-4, 7-8, 12-21, 24-26, 31 and 32 stand rejected under 35 U.S.C. § 102(a) as assertedly anticipated by Andreansky et al. (1998) Gene Therapy, 5:121-130 ("Andreansky").

Claims 1-4, 14, 19-21, 24 and 31 stand rejected under 35 U.S.C. § 102(e) as assertedly anticipated by U.S. Patent No. 6,379,674 ("Rabkin).

Claims 5, 6, 22 and 23 stand rejected under 35 U.S.C. § 103(a) as assertedly unpatentable over Rabkin in view of U.S. Patent No. 5,328,688 ("Roizman '688").

Claims 1, 9-11, 19, and 27-29 stand rejected under 35 U.S.C. § 103(a) as assertedly unpatentable over Andreansky or Rabkin in view of U.S. Patent No. 5,641,651 ("Roizman '651").

Claims 19-31 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly not enabled by the specification.

Claims 20-23 stand rejected under 35 U.S.C. § 112, second paragraph, as assertedly indefinite.

II. Patentability Arguments

A. The Anticipation Rejections

The claims are amended such that the recombinant herpes virus recited therein expresses only one $\gamma_1$34.5 gene copy and comprises an expressible cytokine-encoding DNA. Neither Andreansky nor Rabkin describe such a virus or methods using it to treat neoplastic disease of the central nervous system. Thus, the anticipation rejections should be withdrawn.

B. The Obviousness Rejections

Neither Andreansky nor Rabkin describe or suggest a recombinant herpes virus expressing only one $\gamma_1$34.5 gene copy and comprising an expressible cytokine-encoding DNA. Moreover, they do not decribe using such a virus to treat neoplastic disease of the central nervous system. The secondary references cited within the rejection do not provide motivation to produce or use a virus as claimed. Thus, the obviousness rejections should be withdrawn.

C. The Enablement Rejection

Claims 19-31 stand rejected under 35 U.S.C. § 112, first paragraph, as assertedly not enabled by the specification. The rejection contends that while enabling for certain cytokines such as IL-4, the specification is not enabling for methods of treating neoplastic disease of the central nervous system using other cytokines such as IL-5, IL-10, and TGF-β2. Applicant respectfully disagrees.

As amended herein, claims 19-30 are directed to methods of treating neoplastic disease and are no longer limited to neoplastic diseases of the central nervous system. (New claim 33 specifies that the target tumor is a tumor of the central nervous system.). The claims are amended further to clarify that the expressed cytokine augments tumor cell killing. As discussed in the specification, certain cytokines were known in the art to demonstrate in vivo inhibition of tumor growh by stimulating localized inflammatory and/or immune responses (page 4, lines 20-27). While the IL-10-expressing virus was not functional in the glioma model system exemplified in the specification and described in Andreansky, the art at the time of filing recognized that IL-10 expression inhibited tumor growth in other systems. (See attached Kundu et al. abstract). Moreover, others reported that IL-5 suppresses tumor growth in other systems. (See Masuda et al. abstract). Thus, at the time of filing, those of skill in the art recognized that that cytokines may augment killing of certain tumor cells while being ineffective against other tumors. With this high level of skill in the art along with the teachings of the specification, it would only require routine experimentation to determine whether a particlar cytokine augments killing of a target tumor. Thus, the specification is enabling for the methods of claims 19-30, and 33, along with the pharmaceutical composition of claim 31. Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

D. The Indefiniteness Rejection

Claims 20 and 22 are corrected by amendment herein to properly depend from claim 19. The indefiniteness rejection should be withdrawn.

Conclusion

In view of the above amendments and remarks, Applicant believes the pending application is in condition for allowance.

Dated: December 15, 2004

Respectfully submitted,

By _____

Thomas J. Wrona, Ph.D.
Registration No.: 44,410
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant

Attachments

- Masuda *et al.* Suppression of in vivo tumor growth by the transfection of the interleukin-5 gene into colon tumor cells, Cancer Immun Immunother 41(6): 325-330 (1995) Abstract

- Kundu *et al.* Interleukin-10 gene transfer inhibits murine mammary tumors and elevates nitric oxide, Int J Cancer 76(5): 713-719 (1998) Abstract

Int J Cancer. 1998 May 29;76(5):713-9.

Interleukin-10 gene transfer inhibits murine mammary tumors and elevates nitric oxide.

Kundu N, Dorsey R, Jackson MJ, Guiterrez P, Wilson K, Fu S, Ramanujam K, Thomas E, Fulton AM.

Greenebaum Cancer Center, University of Maryland, Baltimore, USA.

Transfection of cDNA for IL-10 into line 66.1 murine mammary tumor cells results in marked suppression of tumor growth and metastasis. Others have reported that nitric oxide has potent antitumor activity and IL-10 is known to regulate the inducible isoform of nitric oxide synthase (iNOS) expressed in macrophages. We identified nitric oxide production in mammary tumors as indicated by electron paramagnetic resonance detection of nitric oxide-hemoglobin (NO-Hb). IL-10 expression resulted in elevated levels of NO-Hb in mammary tumors. Immunohistochemical examination of mammary tumors for iNOS protein revealed few positively staining cells in parental or control neo-transfected tumors but strong iNOS staining in all IL-10 transfected tumors, consistent with the NO-Hb data. To determine if mammary epithelial tumor cells themselves, express nitric oxide synthase activity, cultured tumor cells were treated with pro-inflammatory cytokines and nitrite accumulation was assessed in the conditioned medium. All IL-10 producing cell lines accumulated uM concentrations of nitrite in response to short term (24 hr) cytokine stimulation. Cells not expressing IL-10 (parental and neo-transfectants) accumulated no nitrite under similar culture conditions. After longer stimulation (48 hr), parental and 66-neo cells accumulated lower amounts of nitrite. IL-10 gene transfer is associated with increased iNOS protein expression and enzymatic activity detected both in vitro and in vivo. Our findings suggest that the antimetastatic and antitumor activity of IL-10 is related to enhanced production of nitric oxide.

PMID: 9610731 [PubMed - indexed for MEDLINE]

Cancer Immunol Immunother. 1995 Dec;41(6):325-30.

Related Articles, Links

Suppression of in vivo tumor growth by the transfection of the interleukin-5 gene into colon tumor cells.

Masuda Y, Mita S, Sakamoto K, Ishiko T, Ogawa M.

Department of Surgery II, Kumamoto University Medical School, Japan.

To investigate the influence of tumor producing interleukin-5 (IL-5) on growth kinetics of tumors, we transduced the murine IL-5 gene into murine colon C26 tumor cells. Two IL-5-secreting clones, low-level IL-5 producer C26-8B and high-level IL-5 producer C26-6F, were established. Both tumors, C26-6F and C26-8B, grew more slowly than the mock C26 tumor, although the in vitro growth rate of these IL-5 transfectants was much the same as that of the mock C26 cells. There was a significantly decreased number of colonies in the lung of mice given C26-6F or C26-8B tumors i.v. than in mice given mock C26 tumors i.v. Moreover, in mice given C26-6F cells i.v., a smaller number of tumor colonies in the lung was observed, as compared to the case with C26-6B cells. While the growth rate of C26-8B tumors in mice treated with anti-IL-5 mAb was more rapid than that seen in control mAb-treated mice, growth of C26-6F tumors in anti-IL-5-mAb-treated mice was slightly more rapid compared to findings in control mAb-treated mice. The isotype-matched mAb did not alter the in vitro growth of mock-C26 cells or of the IL-5-gene-modified C26 cells. Growth of IL-5-secreting C26 tumors transplanted in nude mice was also inhibited. These results suggest that tumor-producing IL-5 inhibits growth of colon tumors mediated through T-cell-independent protective mechanisms of the host.

PMID: 8635189 [PubMed - indexed for MEDLINE]